REMARKS

Information Disclosure Statement:

The Examiner noted that the Patent Office has misplaced the 1449 and reference copies of the Information Disclosure Statements filed on June 18 and June 19, 2000. The Examiner has requested that Applicants resubmit these 1449 forms and reference copies. Enclosed herewith are copies of the requested documents.

Claim Amendments:

The claims have been amended to more particularly describe the present invention and to a certain extent, to recite some of the elected species. More particularly, Claim 1 has been amended to include the limitations of: (a) B cell antigen receptor (supported by original Claim 15); (b) a regulatory compound that is an antibody (supported by original Claim 8); (c) an antibody that binds to the transducer component (supported by original Claim 11); (d) the transducer component comprises an Igα-Igβ dimer (supported by original Claim 16 and page 11, lines 26-28 of the specification); (e) the extracellular ligand binding component is an mIg (supported by original Claim 18 and page 13, lines 20-22 of the specification); and (f) the antibody does not substantially stimulate said B cell antigen receptor (supported by the specification at page 16, lines 11-14; page 17, lines 19-23; page 22, lines 18-19; and page 54, lines 22-23.

The remaining amendments to dependent claims merely place these claims in proper dependent form with regard to amended Claim 1.

Objection to the Specification and Rejection of Claims 1-6, 15-19, 21-22 and 30-33 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has objected to the specification and rejected Claims 1-6, 15-19, 21-22 and 30-33 under 35 U.S.C. § 112, first paragraph. Specifically, the Examiner acknowledges that the specification is enabling for a method to desensitize a receptor by administering the regulatory compounds disclosed on pages 36 and 37 and the monoclonal antibodies disclosed in Example 9. However, the Examiner contends that the specification does not enable one of skill in the art to make and use a representative number of regulatory compounds encompassed by the claims. In addition, the Examiner asserts that the *in vivo* application of a regulatory compound is fraught with technical

difficulties because a protein may be inactivated before producing an effect, it may not reach the target area, or other properties may make the protein unsuitable for *in vivo* therapeutic use.

Initially, Applicants note that, to expedite prosecution, the claims have been limited to many of the elected species, including, the administration of an antibody that binds to the transducer component of the B cell antigen receptor. Therefore, the limitations of Claims 8 and 11, which were not rejected by the Examiner under this section, have been added to Claim 1. Therefore, it appears that the Examiner's rejection under this section is overcome by this amendment. The Examiner has admitted that the specification enables the use of antibodies to desensitize a B cell antigen receptor, and has been exemplified by the antibodies disclosed in the Examples section of the specification. The specification describes in detail how to make antibodies, and particularly, how to make and select antibodies against the Igα-Igβ dimer of the B cell antigen receptor. It is noted that one experiment by the present inventors yielded 2 out of 15 antibodies that had the desired specificity and function, and therefore, Applicants submit that the production of additional antibodies meeting the claim limitations is both within the ability of one of ordinary skill in the art and predictable.

Moreover, given the guidance provided in the specification and the general state of the art at the time of the invention, one of skill in the art would be able to use the antibodies that bind to the transducer component of the BcR in a therapeutic method to destabilize a BcR *in vivo*, *ex vivo* or *in vitro*. At the time of the invention, antibodies had been used *in vivo* and indeed, methods of making antibodies that are less susceptible to inactivation *in vivo* could be produced (e.g., humanized antibodies). Finally, with regard to the Examiner's statement that inhibition of intracellular calcium flux *in vitro* is insufficient to predict *in vivo* immunosuppressive efficacy, Applicants note that receptor desensitization has been characterized *in vivo* (e.g., in transgenic mouse models) by the inability of antigen to elicit renewed Ca^{2+} mobilization despite the continued expression of antigen binding receptors (e.g., see the specification, page 2, lines 9-11). Therefore, this biochemical event, among others, is predictive of the events associated with receptor desensitization *in vivo*. Therefore, Applicants submit that one of ordinary skill in the art could practice the method of the present invention without undue experimentation and with a reasonable expectation of success.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-6, 15-19, 21-22 and 30-33 under 35 U.S.C. § 112, first paragraph.

Objection to the Specification and Rejection of Claims 1-6, 15-29, 21-22, 30-31 and 33 Under 35 U.S.C. § 112, first paragraph:

The Examiner has rejected Claims 1-6, 15-29, 21-22, 30-31 and 33 under 35 U.S.C. § 112, first paragraph, contending that the subject matter of these claims was not described in the specification in a such a way that reasonably conveys to one of skill in the art that the inventors were in possession of the claimed invention when the application was filed. Specifically, the Examiner contends that "regulatory compound" encompasses a substantial variety of subgenera that can be any of a variety of classes of compounds. The Examiner contends that a disclosure of a specific antigen, a specific peptidomimetic and an antibody to the extracellular ligand binding component does not adequately describe the scope of the claimed genus. Moreover, the Examiner submits that a disclosure of two monoclonal antibodies that bind to Igα or Igβ does not describe the scope of compounds that bind to transducer components because transduce components other than Igα and Igβ are used by receptors to transmit signals. The Examiner additionally submits that it is unclear in Example 9 whether Igα or Igβ are bound by the exemplified antibodies, and to what specific region of Igα/Igβ the antibodies bind. Finally, the Examiner asserts that there is insufficient written description of a bi-specific antibody.

Again, it is initially noted that the claims have been limited to many of the elected species, including the limitations of Claims 8 and 11, which were not rejected by the Examiner under this section. Therefore, Applicants submit that Examiner's rejection of the claims under this section is addressed by this amendment. Applicants have described the production and use of two antibodies that bind to an Igα-Igβ dimer of the BcR and since the claims are now limited to a transducer component that is an Igα-Igβ dimer, the Examiner's concerns regarding antibodies that bind to other transducer components is moot.

With regard to the Examiner's statement that it is unclear in Example 9 whether Igα or Igβ are bound by the exemplified antibodies, and to what specific region of Igα/Igβ the antibodies bind, Applicants submit that it is not necessary to know whether Igα or Igβ is bound by the antibodies nor whether the antibodies bind a region more specifically defined than the extracellular domain of the dimer. Rather, it is necessary to know that the extracellular domain of the Igα-Igβ dimer is bound and that such binding results in the dissociation or inhibition of association of the transducer component with the extracellular ligand binding component. The specification has taught one of

skill in the art how to produce such an antibody and how to test for such function. One of skill in the art would have a high expectation of success at using the guidance provided in the specification to make such an antibody. As discussed above, one experiment by the present inventors yielded 2 out of 15 antibodies that had the desired specificity and function, and therefore, Applicants submit that the production of additional antibodies meeting the claim limitations is predictable. Indeed, Applicants note that the Examiner, at page 12 of the Office Action, states that "modification of antibodies having a desired specificity such as for a transducer component was routinely practiced by the ordinary artisan at the time the invention was made"; that "various forms of antibodies, including monovalent antibodies, are obvious variants once an antibody with the desired antigen specificity has been generated" and that "the production of antibodies...to any specific site on a known antigen...was of itself a matter of routine experimentation for the ordinary artisan at the time the invention was made."

With regard to the bi-specific antibodies, Applicants submit that given the identification of the target sites that would be suitable for production of the second binding region of the antibody is sufficient to allow one of skill in the art to produce such an antibody. Again, Applicants note that the Examiner has admitted that the production of an antibody to a specific site on a known antigen was routine experimentation at the time of the invention and further, that modification of antibodies having the desired specificity (which should include the production of a bi-specific antibody) was also routinely practiced. The present specification has provided sufficient guidance as to what should be the specificity of the second site, particularly with regard to B cells, such that the ordinary artisan would be able to produce bi-specific antibodies according to the present invention.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-6, 15-29, 21-22, 30-31 and 33 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 1, 3-4, 7-8, 10, 15-16, 18 and 33 Under 35 U.S.C. § 102(b):

The Examiner has rejected Claims 1, 3-4, 7-8, 10, 15-16, 18 and 33 under 35 U.S.C. § 102(b), contending that these claims are anticipated by Cambier et al. The Examiner contends that Cambier et al. teach a method to desensitize a B cell antigen receptor by contacting the receptor with a compound that causes a dissociation or inhibits the association of the extracellular ligand binding component and the transducer component. The Examiner asserts that the compound of Cambier et

al. is an antibody that binds to the extracellular ligand binding component (mIg). The Examiner states that although Cambier et al. do not address the molecular basis for the receptor desensitization, the courts have held that there is no requirement that those of ordinary skill in the art know of an inherent property.

Applicants traverse the Examiner's rejection of Claims 1, 3-4, 7-8, 10, 15-16, 18 and 33 under 35 U.S.C. § 102(b). Applicants first note that Cambier et al. do not teach or suggest the production or use of an antibody that binds to the transducer component of a B cell antigen receptor (i.e., the Igα-Igβ dimer). Moreover, the antibodies of Cambier et al. are capable of stimulating the B cell antigen receptor (i.e., the antibodies are actually stimulatory antibodies) (see, Cambier et al., page 6494, col. 2, Results, 1st paragraph), whereas the recited antibody does not substantially stimulate the B cell receptor (i.e., is not capable of substantially stimulating the receptor). Therefore, Cambier et al. fail to teach each and every limitation of the claims.

A stimulatory antibody is not a desirable antibody for use in the method of the present invention. Binding of a B cell receptor to a stimulatory molecule, such as an antigen or a stimulatory antibody, can induce receptor desensitization, but such a molecule can clearly also stimulate the B cell receptor under the appropriate conditions, which would lead to undesirable consequences if the stimulatory compound was used *in vivo* (i.e., potential stimulation where immunosuppression was desired). Therefore, a compound that is stimulatory, while it might be useful to study desensitization of a receptor *in vitro*, would not be clinically desirable or useful. Now that the mechanism of receptor desensitization is known by the teachings of the present invention, one of skill in the art can produce regulatory compounds that trap the receptor in the unstable configuration (i.e., where the transducer and extracellular ligand binding components are uncoupled) and thereby induce unresponsiveness to antigen, without the risk of side effects caused by the stimulation of the receptor. As the Examiner admits, Cambier et al. does not address the molecular basis for receptor desensitization and therefore, Cambier et al. does not provide any motivation or suggestion to produce or use an antibody that does not substantially stimulate the B cell antigen receptor, and that binds to the transducer component to cause a dissociation or inhibit the association of the extracellular ligand binding component and the transducer component.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 3-4, 7-8, 10, 15-16, 18 and 33 under 35 U.S.C. § 102(b).

Rejection of Claims 1, 3-4, 7, 15-16, 18, 21 and 33 Under 35 U.S.C. § 102(b):

The Examiner has rejected Claims 1, 3-4, 7, 15-16, 18, 21 and 33 under 35 U.S.C. § 102(b), contending that these claims are anticipated by Vilen et al. The Examiner contends that Vilen et al. teach a method to desensitize a B cell antigen receptor by contacting the receptor with a compound that causes a dissociation or inhibits the association of the extracellular ligand binding component and the transducer component. The Examiner asserts that the compound used by Vilen et al. is a mimetope of a peptide that binds the extracellular ligand binding component. The Examiner further states that although Vilen et al. do not teach that dissociation/inhibition of association is the mechanism underlying the molecular basis for receptor desensitization, the courts have held that there is no requirement that those of ordinary skill in the art know of an inherent property.

Applicants traverse the Examiner's rejection of Claims 1, 3-4, 7, 15-16, 18, 21 and 33 under 35 U.S.C. § 102(b). Vilen et al. do not teach or suggest the production or use of an antibody for receptor desensitization, including an antibody that binds to the transducer component of a B cell antigen receptor (i.e., the Igα-Igβ dimer) to cause a dissociation or inhibit the association of the extracellular ligand binding component and the transducer component, nor an antibody that does not substantially stimulate the B cell antigen receptor. Therefore, Vilen et al. fail to teach each and every element of the claimed invention.

Moreover, Applicants submit that because Vilen et al. do not teach the underlying molecular basis for receptor desensitization, and further because the peptide used by Vilen et al. is a *stimulatory* peptide, Vilen et al. do not provide any suggestion or motivation to one of skill in the art to produce and use an antibody that does not substantially stimulate the B cell antigen receptor, and that binds to the transducer component to cause a dissociation or inhibit the association of the extracellular ligand binding component and the transducer component.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 3-4, 7, 15-16, 18, 21 and 33 under 35 U.S.C. § 102(b).

Rejection of Claims 1-2, 4-8, 10-11, 15-18 and 33 Under 35 U.S.C. § 102(b):

The Examiner has rejected Claims 1-2, 4-8, 10-11, 15-18 and 33 under 35 U.S.C. § 102(b), contending that these claims are anticipated by Nakamura et al. The Examiner submits that Nakamura et al. teach a method to desensitize a B cell antigen receptor by contacting the receptor

with a compound that causes a dissociation or inhibits the association of the extracellular ligand binding component and the transducer component. The Examiner asserts that the compound of Nakamura et al. is an antibody that binds to the Igβ transducer component. The Examiner contends that, although Nakamura et al. do not address the molecular basis for the receptor desensitization, the courts have held that there is no requirement that those of ordinary skill in the art know of an inherent property.

Applicants traverse the Examiner's rejection of Claims 1-2, 4-8, 10-11, 15-18 and 33 under 35 U.S.C. § 102(b). Applicants submit that the antibody of Nakamura et al., although it binds to the Igβ transducer component and was shown to downmodulate BcR expression and inhibition of B cell proliferation, the antibody did not induce receptor desensitization (see Nakamura et al., page 43, col. 1, last sentence). Indeed, the antibody was unable to prevent stimulation of B cells by an anti-IgM antibody (see Fig. 3). The failure of the antibody of Nakamura et al. to induce receptor unresponsiveness or to prevent receptor stimulation indicates that the antibody of Nakamura et al. does not cause a dissociation or inhibits the association of the extracellular ligand binding component and the transducer component, and may actually reduce BcR expression and cell proliferation by a stimulatory property of the antibody through the Igβ transducer. Therefore, Nakamura et al. fail to teach each and every element of the claimed invention.

Moreover, because Nakamura et al. do not appreciate the molecular basis for receptor desensitization, Applicants submit that this reference does provide any suggestion or motivation to one of skill in the art to produce and use an antibody that traps the B cell antigen receptor in the desensitized configuration (i.e., wherein the transducer and extracellular ligand binding components are uncoupled) and that further does not substantially stimulate the B cell antigen receptor.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-2, 4-8, 10-11, 15-18 and 33 under 35 U.S.C. § 102(b).

Rejection of Claims 1, 3-4, 7-8, 10, 15-16, 18-19, 21-22 and 33 Under 35 U.S.C. § 102(b):

The Examiner has rejected Claims 1, 3-4, 7-8, 10, 15-16, 18-19, 21-22 and 33 under 35 U.S.C. § 102(b), contending that these claims are anticipated by Suzuki et al. The Examiner contends that Suzuki et al. teach a method to desensitize a B cell antigen receptor by contacting the receptor with a compound that causes a dissociation or inhibits the association of the extracellular

ligand binding component and the transducer component. The Examiner asserts that the compound used by Suzuki et al. is an antibody that binds to the extracellular ligand binding component (the "Fab"). The Examiner further asserts that Suzuki et al. teach that the treatment of B cells from normal and SLE patients with the antibody to the BcR results in an "inhibitory effect" on antibody secretion by the B cells. The Examiner states that even though Suzuki et al. do not explicitly teach that the "inhibitory effect" they observe is receptor desensitization, no more of a reference is required than that it sets forth the substance of the invention.

Applicants traverse the Examiner's rejection of Claims 1, 3-4, 7-8, 10, 15-16, 18-19, 21-22 and 33 under 35 U.S.C. § 102(b). Suzuki et al. do not teach or suggest the production or use of an antibody that binds to the transducer component of a B cell antigen receptor (i.e., the Igα-Igβ dimer) to cause a dissociation or inhibit the association of the extracellular ligand binding component and the transducer component. The antibody of Suzuki et al. is an anti-Fab antibody that serves to block the antigen receptor from binding to antigen. In patients with SLE, the anti-Fab antibody had no significant immunosuppressive effect (e.g., see page 299, col. 2, top paragraph, and discussion). Therefore, Suzuki et al. fail to teach each and every element of the claimed invention.

The Examiner admits that the "inhibitory effect" observed by Suzuki et al. is not explicitly taught to be receptor desensitization and indeed, Applicants submit that because the antibody of Suzuki et al. is blocking binding of the natural antigen to the receptor, there is reason to conclude that the inhibitory effect observed by Suzuki et al. is not receptor desensitization. An antibody that blocked the antigen binding site would not be likely to be capable of disrupting or preventing the interaction between the transducer component and the extracellular ligand binding component, and therefore, such an antibody does not meet the claim limitations and would not be predicted to be as effective as the antibodies described in the present invention, which actually disable receptor function. Indeed, the antibody of Suzuki et al. was not immunosuppressive when used against B cells from patients with active SLE. The reference of Suzuki et al. does not set forth the substance of the invention, which is the use of an antibody to cause a dissociation or inhibit the association of the extracellular ligand binding component and the transducer component, resulting in receptor desensitization.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 3-4, 7-8, 10, 15-16, 18-19, 21-22 and 33 under 35 U.S.C. § 102(b).

Rejection of Claims 1-2, 4-11, 15-19, 21-22, 3-31 and 33 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1-2, 4-11, 15-19, 21-22, 3-31 and 33 under 35 U.S.C. § 103, contending that these claims are unpatentable over Ways et al. in view of Nakamura et al. and in further view of Vilen et al. The Examiner contends that Ways et al. teach a method for treating autoimmune disease by inhibiting protein kinase C (PKC), and that PKC can inhibit the activation of B cell response mediated through the cross linking of the BcR by blocking downstream effects of the signaling cascade. The Examiner contends that Ways et al. do not teach a method of desensitizing the BcR by contacting the receptor with a regulatory compound that causes a dissociation or inhibits the association of the extracellular ligand binding component and the transducer component, but references the previously stated position with regard to Nakamura et al. and Vilen et al. to allegedly provide this teaching. The Examiner asserts that it would have been obvious to substitute the antibody of Nakamura et al. for the PKC inhibitor of Ways et al. in methods of desensitizing an autoreactive B cell receptor in a patient. The Examiner states that Vilen et al. teaches that receptor desensitization was due to the uncoupling of the receptor from the signal transduction pathway, that PKC is a downstream event in such pathway, but that the PKC branch is only involved in short-term B cell unresponsiveness. Essentially, the Examiner is apparently asserting that one of skill in the art would have recognized that the antibody of Nakamura et al. is more effective than the downstream inhibitor of PKC and therefore would have been motivated to substitute the antibody of Nakamura et al.

Applicants traverse the Examiner's rejection of Claims 1-2, 4-11, 15-19, 21-22, 3-31 and 33 under 35 U.S.C. § 103. First, Applicants submit that the teachings of Ways et al. regarding the inhibition of PKC activation are irrelevant to the teachings of the present invention, and that the method of Ways et al. refer to a completely distinct method of suppressing B cell function. As the Examiner admits, Ways et al. do not teach a method of desensitizing a BcR by contacting the receptor with a compound that causes a dissociation of and/or inhibits the association of the transducer and extracellular ligand binding components. Also by the Examiner's own admission, Vilen et al. teach that long-term B cell unresponsiveness is independent of PKC activation, and therefore, the Examiner's connection of Ways et al. with either of Vilen et al. or Nakamura et al. is unclear and not based on any motivation provided by any of the references.

Second, as discussed above, neither of Nakamura et al. or Vilen et al. teach or suggest each and every element of the claimed invention. Ways et al. does not make up for the deficiencies of these references and therefore, the combination of references as a whole does not teach or suggest the production and use of an antibody that binds to the transducer component of a B cell antigen receptor (i.e., the Igα-Igβ dimer) to cause a dissociation or inhibit the association of the extracellular ligand binding component and the transducer component, and that does not substantially stimulate the B cell antigen receptor.

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-2, 4-11, 15-19, 21-22, 3-31 and 33 under 35 U.S.C. § 103.

Applicants have attempted to address the Examiner's concerns and submit that the claims are in a condition for allowance. In the event that the Examiner has any questions regarding Applicants' position, the Examiner is encouraged to contact the below named agent at (303) 863-9700.

Respectfully submitted,

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